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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/348,354	07/07/99	HAVENGA	M 4123US

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EXAMINER	
CONNELL, Y	
ART UNIT	**PAPER NUMBER**
1633	5

DATE MAILED: 02/01/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/348,354	Menzo Havenga, et al.
Examiner	**Group Art Unit**
Yvette Connell Albert	1633

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-12 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-12 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Notice to Comply Sequence Requirements

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in EPO on July 8, 1998. It is noted however, that applicant has not filed a certified copy of the foreign priority document as required by 35 U.S.C. 119 (b). If the foreign priority document is not in English, a translation should be provided in the event that intervening prior art becomes available.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 5, 7, 8, 9, 10, and 12 are rejected under 35 U.S.C. 112 second paragraph as being vague and indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected because the term "less antigenic" does not specify a baseline. How much "less antigenic" must the adenovirus serotype be to result in a chimeric adenovirus with reduced antigenicity? "Less antigenic" as compared to what?

Claims 4, 10, and 12 are rejected for use of the term "A". The grammar between independent and dependent claims is incorrect because the dependent recites "A" the preamble of the scope is unclear in scope of the independent claim. The indefinite article "A" at the beginning of a preamble is generally used for independent claims, and since the recited claims are dependent claims, the definite article "The" should be used instead of "A".

Claim 5 is rejected because the term "there is essentially no overlap" cannot be ascertained. Does applicant mean there is virtually no overlap or there is minimum overlap or whatever overlap may exist is negligible? The metes and bounds of the claim cannot be determined.

Claim 9 is rejected because the terms "diminished antigenicity" and "relatively low antigenicity" could not be ascertained. Again, "diminished antigenicity" as compared to what? Or "relatively low antigenicity" as compared to what? The metes and bounds of the claim could not be determined.

Claim 10 is rejected because the term "diminished capability" could not be ascertained. The term capable of/ capability means the capacity of a compound or composition to perform some conditional function is merely a recitation of a latent characteristic, the scope of which is unclear.

Claim 12 is rejected as being vague and indefinite by the use of the terms nucleic acid in the second occurrence. One is not sure whether or not this should be singular or plural. Applicant is advised that the plural "nucleic acids" would render the claim less ambiguous.

The transmittal filed with the application refers to a parent CIP in box number 17 of the transmittal. However, neither the oath, nor box number 17, nor the first line of the specification lists a prior US application number. Please clarify and or advise.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821 (a) (1) and (a) (2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the accompanying Notice to Comply.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C.102 that form the basis for the rejections under this section made in this Office action:

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim 1 is rejected under 35 U.S.C. 102 (a) as being anticipated by Gall et al, 1998. Applicant claims a chimeric adenovirus comprising at least a part of a fiber protein of an adenovirus serotype providing the chimeric virus with a desired host range and at least a part of a penton or hexon protein from another less antigenic adenovirus serotype resulting in a less antigenic chimeric adenovirus.

Gall et al teaches the construction of an adenovirus hexon serotype chimera; the Ad5-Ad2 chimera made by the exchange of hexon proteins between closely related serotypes like Ad5 and Ad2. Hence the claimed invention was anticipated by Gall et al, 1998.

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 11 are rejected under 35 U.S.C. 102 (b) as being anticipated by Gall et al, 1996. Applicant claims a chimeric adenovirus comprising at least a part of a fiber protein of an adenovirus serotype providing the chimeric virus with a desired host range and at least a part of a penton or hexon protein from another less antigenic adenovirus serotype resulting in a less antigenic chimeric adenovirus. The hexon, penton and or fiber proteins are chimeric proteins originating from different serotypes.

Gall et al teaches the construction of a chimeric adenovirus consisting of an Ad5 backbone with the Ad7 fiber gene in place of the Ad5 fiber gene. Ad7 is normally tropic for the lower respiratory tract and enters target cells through a receptor pathway different from that used by Ad5. The humoral response to capsid proteins is responsible for limiting adenovirus gene transfer to a single administration. This

neutralizing antibody response is by definition serotype specific and is responsible for blocking successful readministration of the current generation of adenovirus gene transfer vectors, which are primarily based on Ad5. Hence, Ad5 is the more antigenic serotype. Therefore, the claimed invention was anticipated by Gall et al. (2117-2118).

Claims 2-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Stevenson et al, 1997. Applicant claims a recombinant vector derived from an adenovirus comprising at least one ITR and a packaging signal having an insertion site for a nucleic acid sequence of interest, an insertion site for functionally inserting a gene encoding a penton and or hexon protein of a first serotype of adenovirus and an insertion site for a gene encoding a fiber protein of a second adenovirus of a different serotype. Applicant claims a packaging cell for producing the chimeric adenovirus, and a kit of parts comprising a packaging cell and recombinant virus. Applicant further claims a method of producing a chimeric adenovirus having a desired host range and diminished antigenicity to raise neutralizing antibodies. In addition, applicant teaches a recombinant vector where the insertion sites are not only different, but preferably unique restriction sites.

Stevenson et al teaches an adenovirus vector particle with an altered receptor specificity, the chimeric fiber gene construct containing the Ad3 fiber head domain fused to the Ad5 fiber tail and shaft. For the precise replacement of the wild-type Ad5 fiber gene, a shuttle plasmid was constructed, which included the Ad5 fiber gene, E4, and the right inverted terminal repeat (ITR). This shuttle plasmid was used for incorporation of modified fiber genes into the backbone of an adenovirus vector with E1 and E3 deleted, via homologous recombination. The resulting chimeric vector, Av9LacZ4, contains the nucleus-targeted beta-galactosidase cDNA and the Ad3 fiber head domain. The claimed invention was anticipated by Stevenson et al. (4785).

Stevenson et al teaches that the packaging cell used to produce the chimeric adenovirus was the human embryonic kidney 293 cells which were obtained from ATCC. The modified 5TS3Ha fiber cDNA was incorporated into the genome of Av1LacZ4, and adenovirus vector with E1 and E3 deleted encoding beta-galactosidase, by homologous recombination between Av1LacZ4 and the prep5TS3Ha fiber shuttle plasmid to generate the chimeric fiber adenovirus vector referred to as Av9LacZ4, utilizing human embryonic kidney 293 cells, as the packaging cells. The claimed invention was anticipated by Stevenson et al who utilized 293 packaging cells to produce the chimeric adenoviruses. (4783).

Stevenson teaches all the parts of the claimed kit comprising a packaging cell and recombinant vector. HeLa cells were incubated with increasing amounts of Ad5 fiber protein, Ad3 fiber protein competitor prior to transduction with the Av9LacZ4 chimera or Av1LacZ4 vector. The results obtained indicates that transduction of HeLa cells by the Av9LacZ4 chimera is mediated by the chimeric fiber protein which interacts with the Ad3 receptor. Hence, the modification of the Ad5 fiber head domain resulted in a change in receptor tropism of an adenovirus vector. Thus the claimed invention was anticipated by Stevenson et al who showed all the components of the kit .

Stevenson et al discloses that the expected DNA fragments obtained for the chimeric Av9LacZ4 and Av1LacZ4 vectors were diagnostic fragments after ScaI and DraI digestion of the chimeric genomic DNA, indicating the presence of the Ad3 fiber head domain. Thus the claimed invention was anticipated by Stevenson et al who showed that the insertion sites were different, and were in fact unique restriction sites. (4785).

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 -11 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Stevenson et al 1997, in view of Gall et al, 1996.

Applicant claims a chimeric adenovirus, which would render the chimeric adenovirus less antigenic as compared to other chimeric adenoviruses.

Applicant claims a chimeric adenovirus comprising at least a part of a fiber protein of an adenovirus serotype providing the chimeric virus with a desired host range and at least a part of a penton or hexon protein from another less antigenic adenovirus serotype resulting in a less antigenic chimeric adenovirus. Applicant also claims a packaging cell for producing the chimeric adenovirus, as well as a kit of parts comprising a packaging cell and recombinant vector. In addition, applicant teaches a nucleic acid library comprising nucleic acid derived from different adenovirus serotypes.

Gall et al teaches the construction of a chimeric virus consisting of an Ad5 backbone with the Ad7 fiber gene in place of the Ad5 fiber gene. The packaging cell line used in Gall et al was the 293 human embryonic kidney cells (see page 2117).

Stevenson et al also teaches the generation of an adenovirus vector particle with an altered receptor specificity, the chimeric fiber gene construct containing the Ad3 fiber head domain fused with the Ad5 fiber tail and shaft. In addition, it was reported that the infectivity of Ad3 was significantly less than that of Ad5, with Ad3 having a particle/PFU ratio approximately 20 times that of Ad5. Hence the Ad5 serotype is the more antigenic serotype (see page 4785).

Stevenson et al teaches that the packaging cell used to produce the chimeric adenovirus was the human embryonic kidney 293 cells which were obtained from ATCC. The modified 5TS3Ha fiber cDNA disclosed was incorporated into the genome of Av1LacZ4, and adenovirus vector with E1 and E3 deleted encoding beta-galactosidase, by homologous recombination between Av1LacZ4 and the prep5TS3Ha fiber shuttle plasmid to generate the chimeric fiber adenovirus vector referred to as Av9LacZ4, utilizing human embryonic kidney 293 cells as the packaging cells (see page 4783).

Stevenson further discloses that the restriction enzyme sites within the Ad3 fiber head region were different and unique restriction sites as indicated by the diagnostic fragments obtained after ScaI and DraI restriction endonuclease digestion of the chimera. Stevenson teaches a " kit of parts" comprising a packaging cell and recombinant vector. HeLa cells were incubated with increasing amounts of Ad5 fiber protein, Ad3 fiber protein competitor prior to transduction with the Av9LacZ4 chimera or Av1LacZ4 vector.

Stevenson and Gall et al differs from the claimed invention in that they do not teach a nucleic acid library comprising nucleic acids derived from different adenoviral serotypes. However, at the time of the claimed invention, Stevenson et al taught the isolation of genomic DNA from the purified chimeric fiber

At the time the invention was made it would have been prima facie obvious to recognize that selective targeting of cells, especially human cells would have been achieved by using chimeric adenovirus vectors.

One would have been motivated to combine the teachings in the art regarding a major goal in gene therapy research which "is the development of vectors and delivery systems which can achieve efficiently targeted in vivo gene transfer and expression. Vectors are needed which maximize the efficiency and selectivity of gene transfer to the appropriate cell type for expression of the therapeutic gene and which minimize gene transfer to other cells or sites in the body which could result in toxicity or unwanted side effects (Stevenson et al, see page 4788)". Therefore, by constructing and utilizing customized chimeric adenovirus vectors, allows one to selectively target specific cell types, thus fulfilling one major goal of gene therapy.

There would have been a reasonable expectation of success because Stevenson et al demonstrated conclusively that the THP-1 cell line when utilized in gene transfer to the monocyte/macrophage lineage would be more efficient with vectors having the Ad3 tropism than that of Ad5, while in contrast, human coronary artery endothelial cells were transduced more readily with the vector containing the Ad5 fiber vector than with the chimeric fiber vector. (Stevenson et al, see page 4790).

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvette Connell, whose telephone number is 703-308-7942. The examiner can normally be reached on Monday-Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 703-308-0447.

Any inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Yvette Connell

January 25, 2000

JOHN L. LeGUYADER
PRIMARY EXAMINER
GROUP 1800
1600